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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,542	10/07/2004	Neil-Lee Spector	PU4725USW	8482
23347	7590	12/06/2007		
GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY, MAI B475 FIVE MOORE DR., PO BOX 13398 RESEARCH TRIANGLE PARK, NC 27709-3398			EXAMINER ANDERSON, JAMES D	
			ART UNIT 1614	PAPER NUMBER
			NOTIFICATION DATE 12/06/2007	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USCIPRTP@GSK.COM
ROSALIE.M.CHAMBERLAIN@GSK.COM
JULIE.D.MCFALLS@GSK.COM

Office Action Summary	Application No. 10/510,542	Applicant(s) SPECTOR ET AL.	
	Examiner James D. Anderson	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 September 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5 and 25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 June 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 5 and 25 are presented for examination

Applicants' amendment filed 9/24/2007 has been received and entered into the application. Accordingly, claim 5 has been amended and claims 18, 25, and 31-32 have been cancelled.

Applicants' arguments, filed 9/24/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In light of the new 35 U.S.C. § 112, 1st Paragraph (Written Description) rejection being applied against the pending claims, this Office Action is **Non-Final**.

Response to Arguments

Applicant's arguments filed 9/24/2007 have been fully considered but they are not persuasive.

The rejection of claims 5 and 25 as being unpatentable over Carter *et al.* (WO 99/351146) and Dickerson *et al.* (U.S. Patent No. 6,268,391) is maintained for the reasons of record and reiterated below. Applicants argue that the combination of Carter *et al.* and Dickerson *et al.* does not teach or suggest a method of treatment using the particular combination of therapeutic agents as recited in claims 5 and 25 (see Response, page 4). Firstly, it is noted that a "particular combination" of therapeutic agents is not being claimed. What is being claimed is a treatment

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method, comprising administering the compound of Formula (III) and a cRaf-1 inhibitor. No particular cRaf-1 inhibitors are recited in the claims. Secondly, Carter *et al.* provides explicit motivation to combine the compound of Formula (III) with other chemotherapeutic agents for the treatment of breast cancer. For example, Carter *et al.* suggest that the compounds of their invention, which include the instantly claimed compound of Formula (III), can be employed in combination with other chemotherapeutic agents for the treatment of cancer (page 54, lines 8-10). The instantly claimed compound of Formula (III) was demonstrated by Carter *et al.* to inhibit the growth of HB4a (erbB2) mammary cells, as well as BT474 breast cancer cells (page 110, Table 2, Example 29). Dickerson *et al.* provide the motivation to combine an inhibitor of cRaf-1 with other anti-tumor agents for the treatment of cancer (col. 24, lines 36-40). The inhibition of breast cancer cell growth is demonstrated in Table 4 (col. 102). More importantly, Dickerson *et al.* provide the nexus between activation of cRaf-1 and deregulation of tyrosine kinases such as ErbB2 (col. 2, lines 53-58 and 60-63). Accordingly, one skilled in the art would appreciate that inhibition of ErbB2 by the compound of Formula (III) as taught in Carter *et al.* would likely lead to activation of cRaf-1, which could be inhibited by the compounds disclosed in Dickerson *et al.* Thus, one skilled in the art would reasonably expect that combining the compound of Formula (III) and a cRaf-1 inhibitor would be effective in the treatment of breast cancer, especially erbB2 positive breast cancers.

Applicants further argue that they have demonstrated that the method of treatment recited in the instant claims has unexpected results (see Response, page 4, referring to Figures 4 and 5). However, the results shown in Figures 4 and 5 are limited to a specific combination of the compound of Formula (III) (GW 2016) and the cRaf-1 inhibitor GW5074, and thus do not

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demonstrate unexpected results commensurate in scope with the claims, which recite administration of any and all cRaf-1 inhibitors. Further, the experiments are limited to a specific breast cancer cell line *in vitro*, whereas the claims recite *in vivo* treatment of any and all forms of breast cancer. As such, it is not seen that the unexpected results demonstrated are commensurate in scope with the patent protection sought by Applicants.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 25 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for

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Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description"

Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims recite a genus of compounds that is defined only by the receptors of which they are inhibitors (*e.g.*, claim 5). There is insufficient written description of the claimed cRaf-1 inhibitors, other than those compounds as defined by formula IV at pages 62-86 of the specification. Accordingly, other than compounds of formula IV, Applicants have not demonstrated possession of the claimed "cRaf-1 inhibitor" as recited in claim 5.

Aside from the compounds of formula IV disclosed on pages 62-86 of the specification, Applicants provide no direction as to (a) what subset of compounds out of all possible compounds that exist in the art would have been reasonably expected to have activity in inhibiting cRaf-1 and (b) which of those compounds actually *has* activity in inhibiting cRaf-1, without having to execute hit or miss testing practices in order to make such a determination.

Although general techniques such as cellular assays may be known in the art, this fact fails to diminish the amount of experimentation that the skilled artisan would have to undertake

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to even identify, let alone determine the full scope of, the claimed “a cRaf-1 inhibitor” as recited in claim 5, particularly in view of the fact that this genus as a whole is not one that is well-known or well-defined in the art such that the skilled artisan would readily envision those compounds that are within the scope of the claimed genus.

The need for testing amongst varying species of compounds to determine the full scope of the genus of inhibitors instantly claimed demonstrates that Applicants were not in possession of the full scope of the genus now presently claimed. “Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was ‘ready for patenting’ such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention.” Please see MPEP § 2163.

Despite the disclosure of the compounds of Formula IV defined at, *e.g.*, pages 62-86 of the specification, it remains that the specification provides non-limiting exemplification of a solely functional genus of agents that may be used within the context of the present invention. With the exception of compounds of formula IV as defined in the original disclosure, Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other agents that may have any of the disclosed functions, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination

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thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify other agents that may be amenable for use in the present invention, it remains that at the time of the invention, Applicants had not identified such compounds, and, therefore, did not have written description of the full scope of the genus claimed.

Further, though Applicants have limited the claimed agents to those that perform a particular function, e.g., those that inhibit cRaf-1, it remains that Applicants have not appropriately defined the metes and bounds of the genus, even when limited by function (step-plus-function form). As taught in the MPEP at § 2163, step-plus-function claims are not adequately described if "the written description adequately links or associates adequately described particular structure, material or acts to the function recited in a step-plus-function claim limitation," or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a step-plus-function limitation." The instant application fails to meet these criteria. The present specification provides no disclosure beyond the generic disclosure of the required function that would correlate a common structural element or material to performance of the claimed function and that would be readily identifiable to one of skill in the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 5 and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carter *et al.* (WO 99/35146; Published July 15, 1999) in view of Dickerson *et al.* (U.S. Patent No. 6,268,391; Issued July 31, 2001).

Instant claim 5 recites a method of treating breast cancer comprising administering the compound of formula (III) and a cRaf-1 inhibitor.

Carter *et al.* disclose methods of treating human malignancies, including breast, gastric, head and neck, and pancreatic tumors, especially those driven by EGF-R or erbB-2, comprising administering compounds of formula (I) (page 3, lines 4-12; page 3, line 24 to page 13, line 26; page 50, lines 10-17). Preferred compounds of the invention include the instantly claimed compound (page 37, lines 33-34 and page 100, Example 29). Salts of the compounds disclosed in Carter *et al.* are taught at page 40, lines 5-14 and reasonably suggest the instantly claimed monohydrate ditosylate salt of the compound of formula (III) as instantly claimed. Carter *et al.* suggest that the compounds of the invention “and their salts and solvates” may be employed

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alone or in combination with other therapeutic agents for the treatment of cancer (page 54, lines 8-10). For anticancer therapy, combination with other chemotherapeutic, hormonal or antibody agents is envisaged (*id.* at lines 10-11). The reference thus provides explicit motivation to combine the instantly claimed compound with other chemotherapeutic agents for the treatment of cancer. The instantly claimed compound of formula (III) was shown to effectively inhibit the growth of HB4a (erbB2) mammary cells, BT474 breast cancer cells, HN5 head and neck cancer cells and N87 gastric cancer cells (page 110, Table 2, Example 29). HB4a mammary cells transfected with H-ras cDNA were not inhibited by the claimed compound (*id.*).

Dickerson *et al.* disclose compounds that can be used in the treatment of disorders mediated by cRaf1 kinase (Abstract). cRaf1 kinase is deregulated by events that are common in human cancer. For example, ras genes are mutated with the following frequencies in the following representative primary tumors: lung, 30%; colon, 50%; pancreatic, 90% (col. 2, lines 53-58). cRaf1 is also activated by deregulation of tyrosine kinases including, cSrc, ErbB2, EGFR and bcr/abl. These events are associated with breast, colon, and lung carcinomas (*id.* at lines 60-63). Dickerson *et al.* thus provide compounds (col. 4, line 1 to col. 23, line 47) for the treatment of human malignancies, including breast, pancreatic and gastric cancer (col. 3, lines 35-47 and col. 23, lines 49-60). Combination therapy with other known anti-tumor therapies for more effective treatment of such tumors is disclosed (col. 24, lines 36-40). The reference thus provides the motivation to combine an inhibitor of cRaf1 with other anti-tumor agents for the treatment of cancer. The effectiveness of representative compounds of the invention in inhibiting colon, pancreatic, breast and prostate cancer cell growth is demonstrated in Table 4 (col. 102).

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In the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed methods of treating cancer would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The instantly claimed compound of formula (III) and cRaf-1 inhibitors were both known in the art to inhibit the *in vitro* growth of the same cancer cell lines (*e.g.*, breast and pancreatic). Further, Carter *et al.* and Dickerson *et al.* both suggest and provide the skilled artisan with the motivation to combine erbB2 inhibitors (such as a compound of formula (III)) and cRaf-1 inhibitors for the treatment of cancer. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Further, erbB2 inhibitors and cRaf-1 inhibitors have different mechanisms of action and cRaf-1 is activated by deregulation of tyrosine kinases including, cSrc, ErbB2, EGFR and bcr/abl (Dickerson *et al.* at col. 2, lines 60-63). As such, the skilled artisan would have been imbued

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with at least a reasonable expectation that a combination of the compound of formula (III) and a cRaf-1 inhibitor would be an effective treatment of breast cancer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


James D. Anderson
Patent Examiner
AU 1614

November 26, 2007


ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER